Simultaneous Cleavage of N-Tosyl and S-Benzyl Groups in Amino Acid and Peptide by Electrolytic Reduction (Commemoration Issue Dedicated to Professor Minoru Ohno On the Occasion of his Retirement)

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Simultaneous Cleavage of N-Tosyl and S-Benzyl Groups in Amino Acid and Peptide by Electrolytic Reduction[1)]

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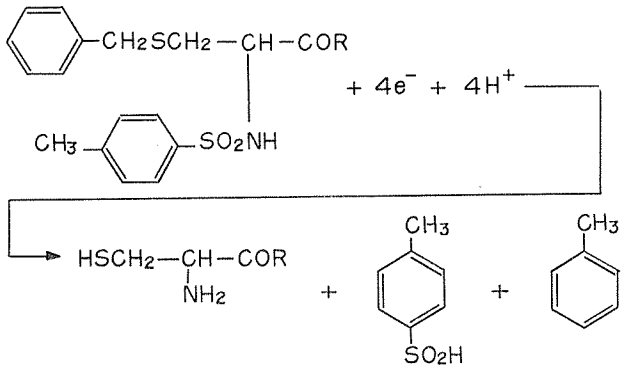
In SH-containing amino acid and peptide, the benzyl group has been widely used for the protection of the thiol group, since du Vigneaud *et al.* demonstrated in 1935 that the S-benzyl group was readily removed by the reductive action of sodium-liquid ammonia (Na/NH_3)[3)]. As another technique, Sakakibara and Shimonishi[4)] reported that the benzyl group in S-benzyl cysteine peptides could be removed by the use of anhydrous hydrogen fluoride. In recent, Ives[5)] found another cleavage method by an electrolysis in liquid ammonia for the removal of S-benzyl group in peptide chemistry.

On the other hand, *p*-toluenesulfonyl (tosyl) group is also useful protecting group for amino group, because the N-tosyl is stable under most conditions. In the removal of the N-tosyl group in amino acid and peptide, Na/NH_3 reduction method has been also employed.[3)] Horner *et al.*[6)] reported the method of electrolytic reductive cleavage of the N-tosyl group by the use of tetramethylammonium amalgam. In most recent, the convenient electrolytic reductive method[7)] was investigated in our laboratory. However, it was also described that cleavage of the S-benzyl group had not been observed in their investigations. Accordingly, Na/NH_3 reduction method still has to be used for the simultaneous removal of S-benzyl and N-tosyl groups.

In this paper, we wish to report that the S-benzyl and N-tosyl groups in amino acid and peptide are removed simultaneously by means of electrochemical method.



(R: OH, or amino acid residue)

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Namely, in the course of studies on the electrolytic reductive cleavage of N-tosyl group,[7] the removal of the S-benzyl group in S-benzyl-N-tosyl cysteine is observed in non-aqueous solvent system. The reductive cleavage reaction would proceed in the above scheme.

The present method involves the fisson of sulfur-carbon bond and sulfur-nitrogen bond in S-benzyl-N-tosyl amino acid by the use of tetramethylammonium chloride (TMA) as an electron transfer agent, mercury as cathode and platinum as anode in absolute methanol. An example of the electrolytic reduction is as follows:

A mixture of 3.45 g of N-tosyl-S-benzyl-L-cysteine, 5.0 g of TMA and 70 ml of absolute methanol was placed in a cathodic compartment with a mercury cathode. The solution in an anodic compartment with a platinum consisted of 3.0 g of TMA and 30 ml of absolute methanol. A membrane was used and current density of 160 mA/cm^2 was passed through the solution at 15–20° with stirring, and then the electrolysis was carried out under an atmosphere of nitrogen for 8 hrs. After the reduction was over, the cathodic methanol solution separated from the cathodic compartment was acidified with hydrochloric acid and then evaporated *in vacuo* under nitrogen atmosphere. The residue was treated with Dowex 50 column (H^+ form) and non-amino acid acidic components were eluted with water, then amino acid was eluted with 5 per cent ammonia. The solution was evaporated to dryness *in vacuo* to obtain the crude cysteine under nitrogen atmosphere. The product was recrystallized from water to afford paper chromatographically and optically pure L-cysteine which was identical with authentic commercial specimen. The yield was 0.92 g (76%). $[\alpha]_D^{25}$ +6.5° (c=2, 5N–HCl) (Lit.[8] $[\alpha]_D^{25}$ +6.0° (5N–HCl)).

This method was also applied for the tripeptide such as S-benzyl-N-tosyl glutathione to obtain physiologically active glutathione in 70 per cent yield.

This procedure is mild enough to form SH and NH_2 free amino acid and peptide with retention of the whole optical activity and with preservation of the peptide bond.

Further investigation is required to clarify the mechanism of the reaction and is currently in progress.

REFERENCES

(1) Formation of optically active amino acid. 2. Part 1; Ref. 7.
(2) To whom the correspondence should be addressed.
(3) V. du Vigneaud, L. F. Andrich and H. S. Loring, *J. Amer. Chem. Soc.*, **52**, 4500 (1930), V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts and P. G. Katsoyannis, *J. Amer. Chem. Soc.*, **76**, 3115 (1954).
(4) S. Sakakibara and Y. Shimonishi, *Bull. Chem. Soc. Japan*, **38**, 1412 (1965).
(5) D. A. J. Ives, *Can. J. Chem.*, **47**, 3697 (1969).
(6) L. Horner and H. Neumann, *Chem. Ber.*, **98**, 3462 (1965).
(7) K. Okumura, T. Iwasaki, M. Matsuoka and K. Matsumoto, *Chem. & Ind.* 929 (1971), T. Iwasaki, K. Matsumoto, M. Matsuoka and K. Okumura, *Bull. Chem. Soc. Japan*, in publication.
(8) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Vol 3, John Wiley & Son, Inc, (1961) p. 1880.